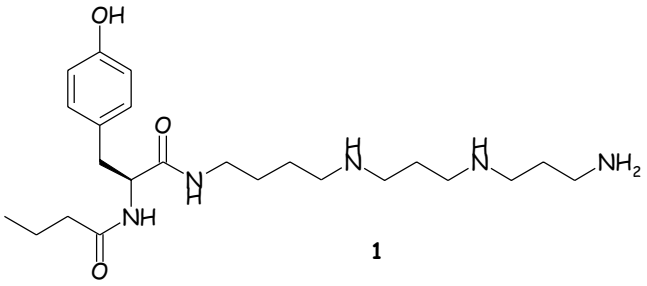
Current literature highlights – August 2001

Philanthotoxin analogues

Philanthotoxins, a group of non-competitive antagonists of ionotropic receptors, are composed of long-chain polyamines connected to a relatively nonpolar head-group via an amide bond. The interest in medicinal chemistry and pharmacology of philanthotoxins has recently been highlighted by the observation that specificity of their antagonist action on various classes of ionotropic receptors can be achieved by modification of the polyamine portion of the molecule. Thus, natural and synthetic toxins (**1**) are known to antagonise various types of nicotinic acetylcholine receptors (nAChRs) and ionotrophic glutamate receptors (iGluRs) with similar potency. On the other hand, analogues in which the secondary amino groups are replaced by methylene groups or oxygen atoms (**2**) exhibit enhanced antagonist activity at mammalian muscle-type nAChR and Torpedo nAChR, while being inactive on several types of iGluR. Previous structure-activity investigations on synthetic analogues containing a symmetrical spermine moiety, or closely related polyamine which have been tested on iGluR and nAChR, emphasise the importance of the hydrophobic character of the headgroup. In contrast, no information about the influence of the structure of the headgroup on the potency of philanthotoxin analogues that lack inner basic sites is available. In an effort to produce Structure Activity Relationships in such series, a library of compounds was synthesised testing whether compounds lacking the inner basic sites bind to nAChR in a similar fashion (Solid-phase synthesis and biological evaluation of a combinatorial library of philanthotoxin analogues, J.W. Jaroszewski *et. al., J. Med. Chem*., 43, (2000), 4526-4533). A library of 18 individual compounds was synthesised on trityl chloride solid phase. Of those compounds tested which lacked the inner basic sites, all were inactive when tested on rat brain non-NMDA receptors. The success of this library protocol lies in the increase in understanding of SAR of antagonism of nAChR by philanthotoxin analogies lacking inner basic sites.



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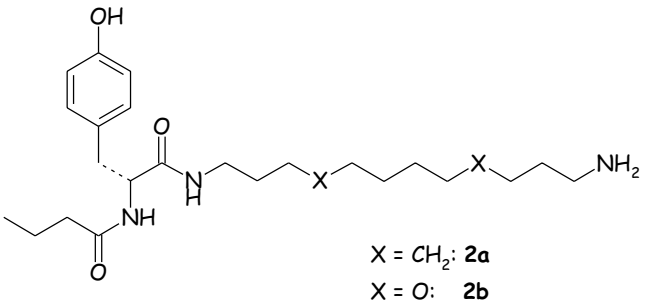
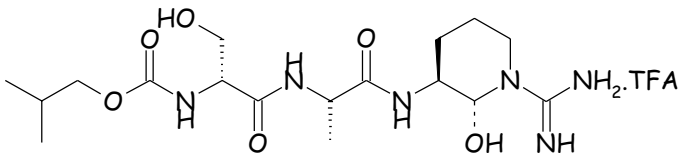


X = CH_2: **2a**

X = O: **2b**

Urokinase inhibitors

Urokinase-type plasminogen activator (u-PA) is one of the two major endogenous plasminogen activators that catalyse the conversion of the zymogen plasminogen to the fibrinolytic protease plasmin. The primary role of u-PA is to generate plasmin in events involving the degradation of the extracellular matrix. Localisation of u-PA on the cell surface is achieved by binding to urokinase plasminogen activator receptor (u-PAR), which is attached to the cell membrane via its glycosyl phosphatidyl inositol (GPI) anchor. Recent advances in the elucidation of the function of the u-PA/u-PAR system have led to an increased understanding of the role played by this enzyme in angiogenesis, cell invasion and cancer metastasis. Efforts are focused on the development of selective direct and mechanism-based synthetic u-PA inhibitors as potential therapeutic targets for cancer, arthritis and pathological angiopathies (Synthesis and biological activity of peptidyl aldehyde urokinase inhibitors, T.G. Nolan *et. al.*, *Bioorg. Med. Chem. Lett.*, 10, (2000), 983-987). A library of eleven peptidyl argininals were synthesised in solution. One of the most potent compounds isolated was **3** which possessed an IC_{50} of 23.1 nM against human urokinase enzyme, with 63 fold selectivity against human plasamin enzyme and >100-fold selectivity against human t-PA enzyme. This work has provided further delineation of the active site requirements of urokinase plasminogen activator and in the discovery of potent and selective inhibitors.



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